REMARKS

Claims 1-41 are pending in this application. Claims 5-8, 12-22, 26-28, and 32-41 have been withdrawn from consideration. Claims 1-4, 9-11, 23-25, and 29-31 have been rejected. Claims 1-41 have been canceled. Claims 42 and 43 have been added. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Election/Restriction Requirement Under 35 U.S.C. §121

While the species election has been withdrawn, the restriction requirement placing the claims into Groups I and II has been deemed proper and made final. Claims 5-8, 12-22, 26-28 and 32-41 have been withdrawn from further consideration. Accordingly, Applicants are canceling claims 5-8, 12-22, 26-28 and 32-41 without prejudice, reserving the right to file continuing applications for the canceled subject matter.

II. Information Disclosure Statement

Applicants acknowledge the Examiner's consideration of the information disclosure statement submitted July 1, 2000.

III. Rejection of Claims Under 35 U.S.C. §101

Claims 1-4, 9-11, 23-25, and 29-31 have been rejected under 35 U.S.C. §101. It is suggested that the rejected claims, as written, do not sufficiently distinguish over 2,5-DKG reductase as they exist naturally. To facilitate the prosecution of the present application, Applicants have amended the claims to

indicate that the claimed mutant 2,5-DKG Reductase A is isolated thereby distinguishing the mutant 2,5-DKG Reductase A from those found in nature. It is therefore respectfully requested that this rejection be withdrawn.

IV. Rejection of Claims Under 35 U.S.C. §112

Claims 1-2, 9-10, 23-24, and 29-30, and claims 3-4, 11, 25 and 31 depending therefrom, have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, it is suggested that the terms "2,5-DKG" and "2-KLG" are not clear.

In an earnest effort to clarify, Applicants have canceled all pending claims and added new claims 42 and 43 to place the claims in better form for consideration. As presented, new claims 42 and 43 read on a mutant 2,5-Diketo-D-Gluconic Acid (2,5-DKG) Reductase A which converts 2,5-DKG to 2-keto-L-gulonic acid. Support for the definition of 2,5-DKG and 2-KLG is found in the specification at page 1, lines 6-10. In light of this clarification, it is respectfully requested that this rejection be withdrawn.

Claims 2-4, 10-11, 24-25 and 30-31 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of the phrase "having an amino acid substitution in position..." It is suggested that because Applicants have not provided a specific amino acid sequence for 2,5-DKG Reductase A, it will be impossible for the Examiner to do a meaningful search of the claim limitations. To specify the structural and functional characteristics of the claimed mutant 2,5-DKG

Reductase A, the newly added claims indicate that the mutant 2,5-DKG Reductase A has an improved rate of converting 2,5-DKG to 2-KLG compared to wild-type 2,5-DKG Reductase A and provides wild-type 2,5-DKG Reductase A set forth in SEQ ID NO:1 as a point of reference. In light of this clarification it is respectfully requested that this rejection be reconsidered and withdrawn.

Claims 1, 9, 23 and 29, and claims 2-4, 10-11, 24-25 and 30-31 depending therefrom, have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reciting the phrases "improved ability to convert 2,5-DKG to 2-KLG", "increased expression" and/or "improved temperature stability". Claims 9 and 29, and claims 10-11 and 30-31 depending therefrom, have been rejected under 35 U.S.C. 112, second paragraph as being indefinite for the recitation of the phrase "2,5-DKG reductase A having increased expression." Claims 2-3, 10-11, 24-25 and 30-31 have also been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reciting the term "having." Claims 1 and 29, and 2-4 and 30-31 depending therefrom, have also been rejected under 35 U.S.C. 112, second paragraph as being indefinite for reciting the term "ability." Applicants respectfully disagree with these rejections.

As indicated in the specification, Applicants have identified key amino acid residues and domains (*e.g.*, residues 165-168, 187-198, 224-234, and 262-278; see page 25, lines 26-33) of 2,5-DKG Reductase A which, when mutated, result in altered characteristics compared to wild-type 2,5-DKG Reductase A (see page 10, lines 24-27). For example, mutation of residue 192 results in an improved rate of conversion of 2,5-DKG to 2-KLG (see Example 5); whereas mutation of amino acid residues 2, 5,

and 7 results in a greater extent of *in vivo* protein accumulation (see Example 6) and mutation of amino acid residues 55 and 57 improves temperature stability (see Example 7) when compared to wild-type 2,5-DKG Reductase A. It is respectfully submitted that in view of the specification the skilled artisan can readily ascertain the functional characteristics of particular mutants of 2,5-DKG Reductase A. Thus, the newly added claims recite that the mutant 2,5-DKG Reductase A with an improved rate of converting 2,5-DKG to 2-keto-L-gulonic acid compared to wild-type 2,5-DKG Reductase A comprises substitutions at amino acid residues 2, 5, 6, 55, 57 and 192 of the wild-type 2,5-DKG Reductase A set forth in SEQ ID NO:1 as supported by the specification at Examples 5-7. In light of this amendment, it is respectfully requested that these rejections be reconsidered and withdrawn.

Claims 1-4, 9-11, 23-25 and 29-31 have been rejected under 35 U.S.C 112, first paragraph, as failing to meet both written description and enablement requirements. It is suggested that the claims encompass mutants of any 2,5-DKG Reductase A obtained from any source, including any or all mutants, recombinants or variants thereof, comprising substitutions at the recited positions and any other amino acid positions. It is suggested that the specification describes one representative species of a mutant of 2,5-DKG reductase having the amino acid sequence of SEQ ID NO:1 consisting of substitutions at positions 2, 5, 7, 55, 57 and/or 192. The Examiner suggests that one species is not enough to be representative of the whole genus and an undue amount of experimentation would be required to produce mutants of any or all 2,5-DKG reductase A obtained from any source, including any

or all variants, mutants and recombinants thereof. Applicants respectfully disagree with this rejection.

As amended, the claimed mutant 2,5-DKG Reductase A requires the functional feature of an improved rate of converting 2,5-DKG to 2-KLG and structural feature of substitutions at amino acid residues 2, 5, 7, 55, 57 and 192 of the wild-type 2,5-DKG Reductase A set forth in SEQ ID NO:1. Thus, the claims as currently presented do not include non-functional mutants. As set forth in *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 USPQ 46, 48 (CCPA 1974), "It is not a function of the claims to specifically exclude... possible inoperative substances..."

Given that Applicants have defined the key residues and regions of the 2,5-DKG reductase which contribute to the expression, stability, and activity of 2,5-DKG reductase A, namely amino acid residues 2, 5, 7, 55, 57, 165-168, 187-198, 224-234, and 262-278 (see page 25, lines 26-33), there is a reasonable expectation that a mutant 2,5-DKG reductase A having amino acid substitutions at 2, 5, 7, 55, 57, and 192 with additional substitutions, *e.g.*, at one or more amino acid residues between 165-168, 187-198, 224-234, and 262-278, will have altered activity compared to wild-type 2,5-DKG reductase A. As acknowledged by the Examiner at page 12 of the Office Action, the amount of experimentation needed to make and screen other variants is not undue. Thus, given the guidance provided by the specification as to amino acid residues which contribute to the expression, stability, and activity of 2,5-DKG reductase A, practicing the full scope of the claims would not require undue experimentation.

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' ... That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Some experimentation, even a considerable amount, is not "undue" if, *e.g.*, it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In this case, the Examiner has not adequately shown that practicing the full scope of the claims would require undue experimentation. The Examiner has suggested that the effect of any single amino acid substitution cannot be precisely predicted in advance. However, the claims are not directed to 2,5-DKG Reductase A mutants with any activity. The claims require that the claimed mutant 2,5-DKG Reductase A has an improved rate of converting 2,5-DKG to 2-KLG compared to wild-type 2,5-DKG Reductase A. Thus, any and all mutants which convert 2,5-DKG to 2-KLG at the same or worse rate than wild-type 2,5-DKG Reductase A are outside the scope of the claims.

The Examiner has conceded that the specification is enabling with respect to the exemplified variants. The Examiner has apparently concluded, therefore, that the specification enables those skilled in the art to use mutants with an improved rate of converting 2,5-DKG to 2-KLG as compared to wild-type 2,5-DKG Reductase A. Since the Examiner has concluded that those skilled in the art could make and use any of these mutants, it follows

that they could make and use other mutants having similar activity. It is therefore respectfully requested that the rejections under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

V. Double Patenting

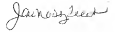
Claims 1-4, 9-11, 23-25 and 29-31 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 5,583,025; claim 1 of U.S. Patent No. 5,376,544; and claim 1 of U.S. Patent No. 5,795,761. Applicants respectfully disagree.

Applicants respectfully point out that the claims as presented herein read on substitutions at amino acid residues 2, 5, 7, 55, 57 and 192 of the wild-type enzyme. In contrast, U.S. Patent No. 5,376,544 claims a mutant 2,5-DKG reductase A enzyme with an arginine substitution at position 192. U.S. Patent No. 5,583,025 draws claim to a mutant 2,5-DKG reductase A enzyme with a plurality of mutations, wherein the presently claimed combination of substitutions is not claimed. Similarly, the 2,5-DKG reductase claimed in U.S. Patent No. 5,795,761 provides substitutions at amino acid residues 21, 22, 23, 24, 25, 46, 47, 48, 49, 50, 51, 52, 164, 169, 170, 199, 200, and 235 of said wild-type enzyme, wherein the presently claimed combination of substitutions is not disclosed. However, in an earnest effort to facilitate the allowance of the claims pending in this case, Applicants file herewith a terminal disclaimer in compliance with 37 CFR 1.321(c).

VI. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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